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(54) Title: WIDE FIELD OF VIEW MICROSCOPE AND SCANNING SYSTEM USEFUL IN THE MICROSCOPE			
<p>(57) Abstract</p> <p>An achromatic, wide field of view microscope system (8) includes a wide field of view optical system (10), a detector (14) positioned to record an image of an object (12) from the optical system, and a computer (16). The optical system is relatively monochromatic and adjustable in response to the signals provided by the computer to focus the image of the object at a wavelength that is selectable from a range of wavelengths while the light delivered to the detector is limited to the selected wavelength. By superposing successive images at different selected wavelengths, an image or composite data set at multiple wavelengths is produced. Various important types of microscopes are shown that incorporate the features described. Of essential importance are scanning microscopes that include scanning mirrors mounted on armatures that are supported by flexure bearing systems or air bearing systems.</p>			

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## WIDE FIELD OF VIEW MICROSCOPE AND SCANNING SYSTEM USEFUL IN THE MICROSCOPE

### Background of the Invention

5        High magnification, commercially available microscopes as used to study cells in medicine typically have a narrow field of view that is far smaller than the area to be viewed. Typically these microscopes have fields of view less than 250 or 500 microns whereas, 10 specimens to be examined are on slides that measure 25 mm x 25 mm or larger. This makes it necessary to shift the field of view many times to carry out microscopic examination of a specimen.

15      In the case of automated scanning microscopes, to study an area larger than the field of view, a driven X-Y stage is employed to take a sequence of X-Y images, in the manner of a raster scan. By employing a lens that has a flat field of view, the adjacent images, or "tiles", are joined at their edges by computer 20 processing, to produce a composite image of the larger area. In order to speed the process, this can be done first at a coarse resolution for panning the area to determine regions of interest, following which one can zoom to higher magnification and finer resolution to 25 enable examination of regions in detail. Though use of commercially available microscopes is effective for examination of optical images, it is slow.

30      In the case of fluorescence and luminescence studies, microscopy is also employed to examine the optical data. An important example concerns fluorescence *in situ* hybridization (FISH) in which cytometry is performed in studies of viruses, chromosomes, DNA, etc. Whereas flow cytometry is available in cases where one reagent is required in the study, flow cytometry is not

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generally useful when using multiple reagents. In the case of multiple reagents, optical microscopy is employed for fluoroscopic examination, using procedures similar to those of imaging microscopes to obtain optical data sets based on fluorescing radiation. Here again, commercially available microscopes, though effective, are quite slow.

The slowness of automated scanning microscopes, in which thousands of adjacent tiles are required to form a composite view, is attributable to the time for acceleration, movement and settling of the mechanical stage between views, which imposes significant limits on the speed with which the automated examination can occur.

The slowness of microscopic examination as practiced with commercially available microscopes has an adverse impact on the efficiency of use of the expensive equipment and the time of the skilled operator. This adversely impacts the cost of health care and limits the use of microscopic analysis.

#### Summary of the Invention

According to one aspect of the invention, I have conceived a new approach to constructing a microscope system that enables practical systems to have far wider fields of view than is common, and which permits much faster microscopic examination of specimens.

According to another aspect of the invention, I have provided scanning system features that enable achievement of preferred versions of new wide field of view microscopes, but which also have important advantages when used in other types of microscopes, and in scanning systems in general where high angular compliance and radial rigidity of an oscillating system are desired.

In respect of the aspect of the invention that concerns wide field of view microscopes, my new approach abandons the use of achromatic objective lenses which are

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commonly used in microscopes of this type. Achromatic lens systems have been employed in the past because of the desire to examine specimens without aberration under white light, or light over a broad band of wavelengths. 5 Achromatic lens systems, however, are expensive, their cost increasing very rapidly with size. Practical cost considerations have been one of the constraints that have limited the field of view of ordinary microscopes.

In place of an achromatic optical system, I employ 10 a monochromatic optical system, i.e. a lens system (reflective, refractive or a combination thereof) that produces an aberration-free image at only a narrow band of a few wavelengths, which, size for size, is much less expensive than is an achromatic lens. Such an optical 15 system is made adjustable to enable selection of the particular wavelength being used at any given time, and to bring the desired focal plane at that selected wavelength into focus. The system is also constructed so that at any given setting, the detector responds only to 20 the wavelength for which the monochromatic optical system is adjusted to be in focus; in fluorescent applications, the detector is made to respond only to the wavelength of interest for the particular examination being conducted.

The adjustability referred to can be provided by 25 use of a single objective lens, and adjusting the component lens elements for each selected wavelength; however, alternatively, if desired, a different objective can be provided for each wavelength as on a turret or slide, and the optical system can be adjusted by 30 positioning the respective objective in position for each wavelength selected.

The resulting microscope system enables practical use of a much larger field of view, which can eliminate the need for an automated mechanical X-Y stage, or can

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limit the number of times the stage needs to be moved during microscopic analysis of a large specimen.

Using my new approach, the need to examine the specimen at more than one wavelength is met by enabling sequential selection of each of the wavelengths of interest, and by computer control, automatically adjusting the system so that the system, in turn, is monochromatic at each of the selected wavelengths. The adjustment not only adjusts the optical system to remove chromatic aberration at the wavelength selected, but also adjusts the focal plane to maintain focus at the desired height. By repeating the adjustment process for each wavelength of interest, a sequence of images or optical data sets at different wavelengths is obtained, by which the desired microscopic examination can be performed.

The need to have a white light image or a single optical data set at a multiplicity of wavelengths beyond the capacity of the monochromatic optical system is also met. The system is programmed to take a sequence of accurately delimited images of the same field of view at different selected wavelengths at the same focal plane, following which these views are calibrated, if necessary, and superposed to provide the desired multi-wavelength image or data set.

In an automated system, superposition of the images is accomplished by computer processing of the image data and correspondingly driving the color system of a high definition video display upon which the superposed images are displayed. In an automated fluorescence or luminescence optical data acquisition, superposition of optical data is accomplished by computer processing of the optical data, and the superposed optical data is presented.

For panning, a microscope system according to the invention samples the data at a coarse rate suitable for

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presenting a panned view of a large area, thus avoiding an undue demand on the memory capacity of the computer. When greater magnification is required, sampling then is done on a pixel by pixel basis, at a diffraction limited spot size, to provide the needed fine resolution of the particular regions that are to be examined in detail. In certain preferred embodiments, a lens system that does not have a highly flat field of view is employed, to take advantage of cost savings that can be made when this constraint is relaxed. This has little adverse influence because there are no flat field requirements for stitching of tiles, as is required for certain commercial microscopes, and the slight sphericity of the overall field of view can have negligible impact on the high resolution inspection of selected small regions of the image.

Out of cost considerations, certain preferred embodiments employ relatively low cost lens systems that have significant spherical aberration. In these embodiments, wide areas of the field of view are inspected only when panning at low resolution at which inaccuracy introduced by the spherical aberration is not a drawback. When viewed at higher magnification, the field of view is much more restricted in width, and over such distance the spherical aberration is minimal. The ability to adjust the focal plane readily accommodates differences in the height of the focal plane between central and peripheral parts of the spherically aberrated field.

It will be seen that the possibility of sharing the data remotely by computer is now made possible in that the data, recorded in digital form, can be sent by modem to anywhere in the world without loss of resolution or cost of ancillary equipment, thus opening the way for

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worldwide consultation in medical and scientific applications.

In respect of the aspect of the invention that concerns scanning systems useful in the above-described 5 microscopes and means generally, I have provided a scanning system in which a moving magnet galvanometer drives a flexure-mounted armature that is mounted on cross-flexures constructed to provide high angular compliance and radial rigidity.

10 Other important features of the invention, employed in preferred embodiments, are given in the following detailed summary.

In general, the invention features an achromatic, wide field of view microscope system including a wide 15 field of view optical system, a detector positioned to record an image of an object from the optical system, and a computer. The optical system is characterized in being monochromatic and adjustable in response to the computer to focus the object at a wavelength that is selectable 20 from a range of wavelengths. The microscope system, for any wavelength so selected, is constructed to limit to the selected wavelength the light delivered to the detector.

In preferred embodiments, the invention features a 25 photo-electric detector for delivering optical data to the computer, and the microscope system includes an optical data recorder. In this case the computer is programmed to cause the object to be imaged at a multiplicity of selected wavelengths in succession, to 30 store image or optical data for each successive wavelength, and to present on the optical data recorder a multi-wavelength visual image or, more broadly, optical data set, free of chromatic aberration based on superposed optical data taken at the respective selected 35 wavelengths. Preferably, the computer is programmed to

view the object at a set of selected wavelengths in succession, the set selected to produce a white light presentation of the object, i.e. a white light image or presentation of fluorescence or luminescence activity of the object.

In preferred embodiments, the invention features a microscope system having an objective lens that is diffraction limited and has a diameter substantially greater than 1 mm.

10 In another aspect, the invention is in the form of a scanning microscope including a driven scanning mirror in the optical system, and the detector is an electronic detector constructed to receive light from the optical system in scanned form and deliver scanned data to the 15 computer. In certain embodiments, the system includes X and Y scanners and the detector comprises a single detector constructed to receive light from the scanning mirrors one pixel at a time. In other preferred embodiments, the detector comprises a linear array of 20 detectors constructed to receive light from a scanning mirror one line of pixels at a time. In other embodiments, the detector comprises light-sensitive film.

25 In another aspect, the invention features a microscope system including an illuminating light source arranged to emit light into the optical system, the optical system being arranged to deliver the light to the object. In other embodiments, a light source separate from the optical system illuminates the object. With either lighting arrangement, it is advantageous to employ 30 a set of filters mounted for selectable insertion in the light path from the light source to illuminate the object at selected wavelengths.

The invention also features a set of filters mounted for selectable insertion in the light path from

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the object to the detector to limit the light delivered to the detector to the wavelength of the filter.

In another aspect, the invention features a microscope system in which the optical system includes a set of lens elements selected and arranged to define an objective lens, a plurality of the lenses in the set being individually adjustable along the optical path in response to the computer, and the computer being so constructed, for any selected wavelength, to adjust the position of the lenses in the set to render the objective lens monochromatic for the selected wavelength while maintaining focus on a selected objective plane. In cases where lens elements are employed that have spherical aberration, adjustment of the focus when viewing at fine resolution is effective to overcome adverse effects of the aberration. In certain embodiments, the objective lens has a field of view greater than 500 microns.

In other aspects, the achromatic, wide field of view microscope described above is combined with an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis, as set forth in the following summary of the novel scanning features.

In another aspect, the invention features a scanning microscope system in which one or more scanning mirrors are disposed on armatures that are supported by flexure bearing and air bearing systems.

In general, in another aspect, the invention features a scanning system in which an optical scanning element is disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis. The armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity. The galvanometer is of the moving magnet type having a

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permanent magnet rotor secured in driving relationship to the armature.

In certain embodiments, the optical element is part of an optical system of a scanning microscope. In other embodiments, the armature is elongated and the flexures are spaced apart pairs of crossed flexures, each flexure being radially rigid. In other embodiments, the flexures of each pair pass through and cross the axis of rotation.

10 In certain embodiments, the armature is balanced statically and dynamically along its axis of rotation by the cross flexures. In other embodiments, the armature has an elongated structure extending continuously between the pairs of flexures.

15 In another aspect, the invention features a scanning system in which a flexure-mounted armature is driven by a galvanometer to rotate about an axis. The armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity. The 20 galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to the armature, the armature being elongated. The flexures are spaced apart pairs of crossed flexures, each flexure being radially rigid and passing through and crossing the 25 axis of rotation.

30 In another aspect, the invention features a scanning system in which an optical scanning element is disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis. The armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity. The galvanometer is of the moving magnet type having a permanent magnet 35 rotor secured in driving relationship to the armature, the armature being elongated. The flexures include spaced apart pairs of crossed flexures, each flexure

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being radially rigid. The flexures of each pair pass through a cavity within the armature and cross the axis of rotation. The armature has an elongated structure extending continuously between the pairs of flexures and is balanced statically and dynamically along its axis of rotation by the cross flexures.

In certain embodiments, the rotor of the galvanometer is polarized into two semi-cylindrical poles on opposite sides of the axis, and the galvanometer 10 includes coils disposed on opposite sides of the magnet, separated by a plane of symmetry that is in essential alignment with the poles of the magnet at the center of its range of rotation, whereby when a current flows through the coils the magnetic field produced applies a torque to the magnet to move it a controlled distance.

In certain embodiments, a sensor rotor is secured to the end of the armature opposite from the galvanometer, to determine the angular position of the armature for comparison to the command input to the 20 system. In other embodiments, an optical element on the armature is part of an optical system of a scanning microscope. In still other embodiments, the sensor rotor is used to control the galvanometer in accordance with the command input to the system.

25 Brief Description of the Drawings

Fig. 1 is a diagrammatic view an illustrative embodiment of the microscope system;

Figs. 2, 2a, and 2b are diagrammatic views of optical arrangements of embodiments of the invention;

30 Figs. 3 and 4 are a block diagram and a diagrammatic view, respectively, of another embodiment of the microscope system;

Figs. 5 and 6 are a block diagram and a 35 diagrammatic view, respectively, of another embodiment of the microscope system;

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Figs. 7 and 8 are a block diagram and a diagrammatic view, respectively, of another embodiment of the microscope system; and

Fig. 9 is a diagrammatic, exploded view of a flexure-mounted scanner, while Fig. 10 is a view of a scanner armature.

#### Description of the Preferred Embodiments

Fig. 1 illustrates certain broad aspects of the invention. Microscope system 8 has an optical system 10 that comprises a series of lenses, two shown for example as lenses 22 and 24, and a stage elevator 20. Upon the elevator 20 and in front of the lenses 22 and 24 lies a stage 18, on which an object 12 is placed. The lenses 22 and 24 are included in the objective lens 26 of the microscope 8. Light from the object 12 is focused by the objective lens 26 along optical path 28 upon a detector 14.

The optical system 10 is monochromatic, made so by choice of a relatively inexpensive monochromatic lens assembly that preferably has a wide field of view. In this embodiment, a filter wheel 30 is provided having a number of filters that are selectable to restrict the light reaching the detector 14 to the selected wavelength that is in focus upon the detector 14. Thus, although the object 12 is illuminated with white light, the detector 14 receives only a monochromatic portion of the image.

Detector 14 is shown generically. For certain embodiments it may be composed of a large two-dimensional aggregate of sensors such as a CCD camera or a focal plane array and capture the entire field of view. In other cases, the detector may be a linear array of light sensors and the field of view may be scanned about one axis by a scanner (not shown), to enable capture of the entire field of view. In other arrangements, the

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detector may comprise either a relatively small two-dimensional or one-dimensional array of sensors combined with two-dimensional scanning.

In important cases of high resolution, the 5 detector is a single point light sensor, such as a single photon multiplier tube, and the field of view is scanned in two dimensions to enable the capture of the entire field of view.

Two-dimensional scanning (see Fig. 4) permits 10 focusing a diffraction limited lens with a very small spot size, on the order of a half micron. The scanning proceeds pixel by pixel over the object to create a wide field of view. To create the appropriate diffraction limited effect, the light beam entering the objective 15 lens has a diameter on the order of 15 to 30 mm. To obtain a small spot size, a large light beam is required.

From the foregoing, it can be seen that many different sensor arrangements are possible and have advantageous applications in particular circumstances.

20 In its broadest aspects, the invention is not limited to electronic detection. Alternatively, the detector comprises a camera which can receive a complete monochromatic image of the object 12 for exposure to a light-sensitive substance such as a photosensitive film.

25 We turn now to the operation of the embodiment of Fig. 1. At the selection of an operator or programmed command, a computer 16 determines wavelength  $\lambda_1$  to be detected by the detector 14 at a particular time. Suitable adjustment commands are delivered to the optical 30 system 10. Responsive to those commands, the relative spacing of the elements of the optical system 10 are adjusted to their  $\lambda_1$  position so that the system is monochromatic at that selected wavelength and is focused so that an image of the object 12 at that wavelength reaches detector 14. The computer also commands stage 18

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to locate object 12 to the axial position associated with  $\lambda_1$  and the filter wheel 30 to move the  $\lambda_1$  filter into alignment with the optical axis so that only light of wavelength  $\lambda_1$  reaches the detector. Later, when imaging at wavelength  $\lambda_2$  or  $\lambda_3$ , respective monochromatic filters in the filter wheel 30 are placed in front of the opening 32 of the detector 14 for selecting the respective wavelength of light to be focused by the optical system 10. Alternatively, filters may be placed in front of the source of white light (not shown).

The image data of wavelength  $\lambda_1$  received by the detector 14 is sent to the memory 17 of the computer 16 for storage and processing. The image data may be stored or combined in a memory buffer. Subsequently, when it is desired to detect an image at another wavelength  $\lambda_2$ , the computer adjusts stage 18 and the lens system to the  $\lambda_2$  position shown diagrammatically in dashed lines, and brings filter  $\lambda_2$  into alignment with the optical axis, and so on. A white light image can thus be obtained by imaging at three selected wavelengths (e.g. red, green and blue), and causing the computer 16 to superpose those images via the color control system of the video monitor 19. This is simply done since conventional color video monitors are based upon superposed images of three colors, and thus are readily adapted to receive the image data from computer storage. By so arranging the microscope to receive monochromatic light for each image, the effects of chromatic aberration by the relatively inexpensive wide field of view objective lens 26 are avoided. Thus, a white light image is reconstructed without regard to chromatic aberration by the relatively inexpensive wide field of view objective lens. Likewise, microscopes of the invention can be employed to form monochromatic images or data sets over a wide wavelength band, or composite images or data sets can be formed at

various combined wavelengths as is commonly required for fluorescence or luminescence microscopy.

The elements of the optical system 10 are adjustable along the optical path 28 to permit focusing of the image at the selected wavelength. In particular, the distances between the stage 18 and each of the lenses 22 and 24 are set to permit the monochromatic portion of the image of the object 12 to be focused upon the detector 14. In this example, the lenses 22 and 24 are separated from the platform 20, and thus from each other, by distances  $D_1$  and  $D_3$ , respectively, which are selected to cause focusing of monochromatic light of wavelength  $\lambda_1$  in the optical system 10. When the image at wavelength  $\lambda_1$  has been detected, the lenses 22 and 24 are then moved to distances  $D_2$  and  $D_4$  to focus monochromatic light of wavelength  $\lambda_2$  in the optical system 10, and so on. The lenses 22 and 24 are moved on conventional threads or cams or on a linear stage (not shown) within the microscope objective 26, driven by appropriately selected stepper motors or actuators (not shown) controlled by the computer. Very fine movement of the optical elements, on the order of tens of microns, may be appropriate and can be readily realized. Advantage is taken here of existing electro-mechanical technology that is conventionally used for making lens systems automatically adjustable.

Further, the stage 18 itself may be moved by elevator 20 to assist in focusing the monochromatic light.

As shown in the examples of Figs. 2, 2a and 2b, there are many important embodiments of the invention, which in each case can employ lenses of wide field of view to the extent desired. For example, in a conventional type of microscope (Fig. 2), the object 12 is illuminated by light source 36 at a position spaced from the optical axis. The appropriately adjusted

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objective lens 26 then refocuses the monochromatic image of the object on an image plane 38 beyond the filter 30.

A scanning microscope of the conventional type (Fig. 2a) is constructed by focusing the light from an external source 36 through a condenser lens 40 onto a point on the object 12. The point on the object 12 is then refocused by the appropriately adjusted objective lens 26 through the wavelength selective filter 30 upon a point in the detector 14. In this case, the stage 18 is moved in the X-Y plane, as shown, so that the objective lens can focus on consecutive points of the object. In such a scanning microscope, the process of illuminating a point on the object and refocusing an image of the object at a point in the detector 14 is repeated to cover an area of the surface of the object 12, and then the individual monochromatic point images are pieced together on the screen 19 of the computer 16 for viewing either at the selected wavelength or combined with images or data sets of other wavelengths. Thus, a scanning microscope can create a wide field of view upon storing a sufficient number of individual point images or data sets in the computer memory.

In a confocal microscope, an objective lens and a collector lens both focus on the same image plane. For example, in confocal scanning microscope (Fig. 2b), the objective lens 26 focuses the image of a point on the object 12 at the image plane 38. The point image on the image plane 38 is then refocused by a collector lens 42 through the wavelength selective filter 30 upon a point in the detector 14.

As has thus been suggested, various types of microscopes, whether conventional or confocal, whether based on reflection or transmission of light, whether scanning or imaging the entire object 12, etc., advantageously employ broad aspects of the invention.

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Figs. 3 and 4 show a wide field of view, point scanning microscope according to another embodiment of the invention.

Light source 52 is a mercury lamp which emits light containing a large number of different wavelengths at different intensities. The light emitted from the light source 52 is focused into a beam by a collimator 54, which is adjusted automatically or manually.

The collimated achromatic light is first passed through a filter on a neutral density filter wheel 54 to control the intensity of the light entering the optical system.

The attenuated light passes through a filter on a broad band pass filter wheel 58, which limits the transmitted light to the chosen wavelength, before reaching a dichroic beam splitter 60. The dichroic beam splitter 60 is partially transmissive and partially reflective, permitting a portion of the light to pass through it to the optical elements of the scanning microscope.

The optical elements of the system 50 include a relay lens 62 and an objective lens 64. The optical elements focus both the light which illuminates the sample 56 and the light to be collected as an image along the same optical path. The objective lens 64 is adjusted according to the principles that have been discussed above using a motor 66. This positions the optical elements of the objective 64 for color focus correction, i.e. for chromatic aberration, at the chosen wavelength of light. The motor 66 rotates a portion of the objective 64 which sets the separation of the optical elements within the objective piece on the basis of instructions received from computer 68.

The objective lens 64 focuses light onto the location of interest on the sample 56 and collects

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reflected light and directs it to the detector. The relay lens system 62 may also be used for fine adjustment and to accommodate variation in the thickness of the sample 56, which may vary as much as 0.5 mm. To ensure that the focal plane of the objective lens 64 is at the proper depth, the light beam is adjusted by moving the sample 56 with respect to the objective lens 64 (for gross movements) or by adjusting the position of the lenses in the relay 62. The computer 68 instructs the operation of a motorized driver (not shown) to adjust the lenses of the relay 62.

The scanning mechanism, as seen in Fig. 4, is configured as a paddle scanner. The light path is shifted from pixel to pixel in the X and Y directions on the sample by rotating separate mirrors 70 and 72, each of which is driven by a respective limited rotation motor controlled by the computer 68. In this embodiment, the sample 56 rests on a stage 74.

As each pixel on the sample 56 is scanned, the light focused as the image is reflected out of the incoming optical beam path by the dichroic beam splitter 60. The imaged light passes through a filter on a narrow band pass filter wheel 74 that selects the monochromatic wavelength of light to be detected.

In certain selected instances, when incoming light of the appropriate wavelength reaches the sample 56, it stimulates emission of light at a different wavelength which it is desired to detect as in fluorescence and luminescence studies. In such instances, the narrow band pass filter 74 is selected to pass light at the fluorescent or luminescent wavelength, which differs from the wavelength selected by the broad band pass filter 58.

In this embodiment, an eyepiece lens 76 focuses the monochromatic imaged light onto a point at the plane of a pinhole 78, the eyepiece 76 being adjustable

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manually or under computer control for fine focusing of the small spot. A small pinhole 78 provides the best signal to noise ratio for a detected signal, since ambient light above and below the focal plane does not 5 pass through the narrow pinhole 78. Pinhole 78 also permits separate imaging of objects at different depths in the sample 56, such as overlapping chromosomes in a cell sample.

If a larger depth of field of the collected image 10 is desired, a larger pinhole is used or none is used, with corresponding trade-offs of signal to noise ratio.

A photo-multiplier tube 80 or other optical sensor placed behind the pinhole 78 detects the focused light. The electrical signal output of the photo-multiplier tube 15 is digitized and stored in computer 68 for later recall to construct the raster scanned image. It is realized that the photo-multiplier has different gain ratios at different wavelengths that may affect the result. The computer stores predetermined, stored gain ratio 20 information, and employs this information to calibrate the recorded data at the selected wavelength of light before reconstructing the achromatic image from the monochromatic data collected by the scanning microscope of Figs. 3 and 4.

25 Referring now to Figs. 5 and 6, a wide field of view linear array scanning microscope according to the invention is shown, adapted to produce white light images.

Light from a white light source 92 is focused into 30 a beam by a collimator and spacial filter 94 before entering an optical system 90. The white light is reflected from a turn mirror 96 under the stage to illuminate an area 98 of the sample 56 from below. The sample is placed on an X-Y-Z stage 100 which has a robot 35 interface with computer 68. The stage 100 is moved in

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three directions, in the Z direction to assist in focusing the image of the sample 56 and in the X and Y directions for scanning the sample.

As in the embodiment of Figs. 3 and 4, a motor 66 controlled by the computer 68 adjusts objective lens 64 for primary focusing of light at the selected wavelength, either red, blue or green. Although it is monochromatically focused, the objective lens 64 transmits a focused white light image of the sample 10 through the optical system 90. The white light image is then reflected by a scanning mirror 102, which scans the sample and transmits the focused image along the remainder of the optical path for detection.

The monochromatically focused image is passed 15 through one of the red, blue or green filters of a filter wheel 104, which is rotatable to select the appropriate monochromatic filter for the wavelength selected to be focused by the objective 64. A detector lens 106 focuses the monochromatically imaged light onto a focal plane 20 inside a linear CCD array detector 108. The linear array collects a series of pixels of monochromatic data at a time. Typically, such array may have from 60 to 8,000 pixels.

The signal collected by the linear CCD array is 25 subjected to signal processing 110 and proceeds to data processing 112. The detection process is repeated for the two remaining monochromatic filters on the filter wheel 104 so that the computer may reconstruct a white light image from the data for the three stored 30 monochromatic images.

Figs. 7 and 8 show a wide field of view scanning microscope employing two dimensional array detection according to another embodiment of the invention.

White light enters the optical system 120 from a 35 source (not shown) above the sample 56. On the basis of

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instructions from the computer 68, a motor 66 adjusts the objective lens 64 to focus a white light image of a wide area of the sample 56 with respect to only one wavelength. The focused light is limited to the chosen wavelength by passing the white light image through the selected sector of a red-green-blue filter wheel 124. A detector lens 106 focuses the monochromatic imaged light onto a focal plane inside a two-dimensional array detector 122.

10 The detector 122 contains a two-dimensional CCD array at the focal plane of the detector lens 106, which detects an image of a planar area of the sample 56. In this embodiment, the signals collected by the two dimensional array are processed in the detector 122 and 15 sent to the computer 68 for storage and data processing 112 so that a white light image can be reconstructed from stored data for the red, green and blue monochromatic images.

20 In other embodiments, the detector comprises a limited dimension two-dimensional array of detectors, such as a two-dimensional miniature CCD array, to collect image data from a small region of the sample. This miniature array is raster scanned across the sample. Thus, the image can be selected and collected by the 25 miniature array with a high level of detail, without raster scanning every point on the sample. Software for utilizing miniature CCD array image data is known in the television industry and can readily be adapted for this microscope scanning function.

30 In still other embodiments, a turret or slide carrying a number of monochromatic objective lenses can be brought into selected position for each selected wavelength to form the monochromatic images or optical data sets.

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For high repeatability and calibration, the microscope system is constructed to be extremely stable, particularly with respect to the high speed scanning mirrors of embodiments involving scanning. Referring to 5 Figs. 9 and 10, it is found that a flexure mounted armature 136 driven by a galvanometer 150 achieves sufficient repeatability and stability in driving the high speed X-axis scanning mirror, so that successive monochromatic images can be superposed to produce useful 10 microscope images.

An armature 136 comprising the rotor is extremely rigid and is balanced statically and dynamically along its axis of rotation by cross flexures 138. Each cross flexure is securely held in place by a flexure support 15 139 mounted to a stable surface. The flexures pass through and cross the armature 136 along its axis of rotation which creates a very rigid structure and permits large rotational movement of the armature about that axis. The flexures have high angular compliance while 20 maintaining high radial rigidity, to provide a high radial mode resonant frequency.

The armature 136 is rotated by the movement of a cylindrical magnet 130 attached to one end of the armature. The magnet 130 is polarized into two 25 essentially semi-cylindrical poles (N and S) on opposite sides of its axis. The magnet 130 is disposed inside the shell 134 of a driver 135. Coils 132 are disposed on opposite sides of the magnet, separated by a plane of symmetry that is in essential alignment with the poles of 30 the magnet 130 at the center of its range of motion. When a current flows through the coils 132, the magnetic field produced applies a torque to the magnet 130 to move it to a controlled position, which rotates the attached armature 136 about its axis. Reference is made to U.S.

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Patent No. 5,225,770 for the details of such moving magnet galvanometers.

An output shaft 142 connected to the X-axis mirror 144 and a "butterfly" sensor rotor 140 are 5 securely attached to the other end of the armature 136. The plates of the sensor rotor 140 are suspended between the stationary capacitive plates of a position sensor (not shown) so that the capacitance varies between the capacitive plates as the armature rotates, such as in a 10 variable capacitance transducer. The sensor rotor 140, being disposed on the end of the armature opposite from the drive, is thermally isolated from the driver 135 to minimize the effects of temperature on transducer 15 measurements. The capacitance signals produced between the plates of the position sensor are amplified and processed into a sum and difference signal. The difference signal determines the angular position of the armature 136 and is compared to the transducer's command 20 input. The sum signal is used as a reference to compensate for the temperature dependence of some of the 25 parameters of the rotor system.

Mirror drivers of this description are preferably employed from the X and Y scanning stages of X-Y scanners. It is presently preferred to employ flexure 25 mounted moving magnet scanners that are available from General Scanning Incorporated, models FM2 and FM3. In certain other instances, other high accuracy bearing systems, such as the known air bearing systems, may support armatures of scanners that are utilized.

30 The microscopes of the present invention achieve a high resolution with respect to the size of the field of view. For example, for single point detection using the raster scanning technique, a 0.5 micron spot size is focused over a 5 mm diameter field of view. For a linear 35 array detector, a 1 micron spot size is focused over an 8

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millimeter square field of view. For a full imaging device, the resolution achieved is a 2 micron spot size focused over a 30 mm field of view.

The images or optical data sets may be recorded 5 and presented by any of a wide variety of optical data recorders, including video monitors, printers, floppy discs for computerized presentation and film recorders.

The specific parameters and choice of equipment for practical microscopes can be selected appropriate to 10 the particular conditions desired to be achieved. These and other features and advantages of the invention will be understood from the drawings and the following claims.

## CLAIMS

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1. An achromatic, wide field of view microscope system comprising:

an optical system, a detector positioned to record an image of an object from said optical system and a computer,

said optical system characterized in being monochromatic,

said optical system being adjustable in response to said computer to focus said object at a wavelength 10 that is selectable from a range of wavelengths,

and said microscope system, for any wavelength so selected, constructed to limit to said wavelength the light delivered to said detector.

2. The microscope system of claim 1 wherein said 15 detector is an photo-electric detector for delivering optical data to said computer, and said microscope system includes a data recorder, said computer being programmed to cause the object to be imaged at a multiplicity of selected wavelengths in succession, to store optical data 20 for each successive wavelength, and to present on said optical data recorder a multi-wavelength optical data set free of chromatic aberration based on superposed optical data taken at the respective selected wavelengths.

3. The microscope system of claim 2 wherein said 25 computer is programmed to view the object at a set of selected wavelengths in succession, the set selected to produce a white light presentation of said object.

4. The microscope system of claim 1 having an 30 objective lens that is diffraction limited and has a diameter substantially greater than 1 mm.

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5. The microscope system of claim 1, 2, 3 or 4 in the form of a scanning microscope, including a driven scanning mirror in said optical system, said detector being an electronic detector constructed to receive light from said optical system in scanned form and deliver scanned data to said computer.

6. The microscope system of claim 5 including X and Y driven scanning mirrors and wherein said detector comprises a single detector constructed to receive light from said scanning mirrors one pixel at a time.

7. The microscope system of claim 5 wherein said detector comprises a linear array of detectors constructed to receive light from a scanning mirror one line of pixels at a time.

15 8. The microscope system of claim 5 wherein said mirror is disposed on an armature supported by a flexure bearing system.

9. The microscope system of claim 5 wherein said mirror is disposed on an armature supported by an air 20 bearing system.

10. The microscope system of claim 1 wherein said detector comprises a light-sensitive film.

11. The microscope system of claim 1, 2, 3 or 4 including an illuminating light source arranged to emit 25 light into said optical system and said optical system arranged to deliver the light to said object.

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12. The microscope system of claim 11 including a set of filters mounted for selectable insertion in the light path from said light source to illuminate said object at a selected wavelength.

5 13. The microscope system of claim 1, 2, 3 or 4 including a light source separate from said optical system for illuminating said object.

10 14. The microscope system of claim 13 including a set of filters mounted for selectable insertion in the light path from said light source to illuminate said object at a selected wavelength.

15 15. The microscope system of claim 1, 2, 3 or 4 including a set of filters mounted for selectable insertion in the light path from said object to said detector to limit the light delivered to said detector to the wavelength of said filter.

20 16. The microscope system of claim 1, 2, 3 or 4 wherein said optical system includes a set of lens elements selected and arranged to define an objective lens, a plurality of said lenses in said set being individually adjustable along the optical path in response to said computer, said computer constructed, for any selected wavelength, to adjust the position of the lenses in said set to render said objective lens 25 monochromatic for said selected wavelength while maintaining focus on a selected objective plane.

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17. The microscope system of claim 11 wherein said set of lens elements has spherical aberration, adjustment of the focus when viewing at fine resolution being effective to overcome adverse effects of such aberration.

18. The microscope system of claim 16 wherein said objective lens has a field of view greater than 500 microns.

19. The microscope of claim 1 including a multiple wavelength light source characterized in that it produces different intensities at different wavelengths of light selectable by said microscope, and including a neutral density filter system constructed to reduce the intensity difference in illumination at said selectable wavelengths.

20. The microscope of claim 1 wherein said detector is a photo-electric detector characterized in that it has different gain characteristics at different wavelengths of light selectable by said microscope and including a gain compensation system for adjusting the value of detected signals in accordance with said gain characteristics to reduce variation in images at different selected wavelengths attributable to said gain characteristics.

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21. An achromatic, wide field of view scanning microscope system, comprising:

- an optical system, a detector positioned to record optical information from said optical system and a computer,
- said optical system characterized in being monochromatic,
- said optical system being adjustable in response to said computer to focus said object at a wavelength that is selectable from a range of wavelengths,
- and said microscope system, for any wavelength selected, constructed to limit to said selected wavelength the light delivered to said detector,
- said detector being an electronic detector for delivering optical data to said computer,
- and said microscopic system including a data recorder,
- said computer being programmed to enable said system to view the object at a multiplicity of wavelengths in succession, to store optical data for each successive wavelength, and to present on said data recorder a multi-wavelength data set, comprising superposed optical data at the respective wavelengths,
- said microscope system including X and Y scanning mirrors in said optical system, and said system including a set of filters mounted for selectable insertion in the light path from said object to said detector to limit the light delivered to said detector to the wavelength of said filter.

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22. The microscope system of claim 1 or 21 further comprising an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis, wherein said armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature.

10 23. The microscope system of claim 1 or 21 further comprising an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis, wherein said armature is mounted on cross-flexures in a manner to 15 provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature; and wherein said optical element comprises part of 20 said optical system.

24. A scanning system comprising an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis, wherein said armature is mounted on cross-flexures in a 25 manner to provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature.

25. The scanning system of claim 22, 23 or 24 30 wherein said armature is elongated, and said flexures comprise spaced apart pairs of crossed flexures, each said flexure being radially rigid.

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26. The scanning system of claim 25 wherein said flexures of each pair pass through and cross said axis of rotation.

27. The scanning system of claim 26 wherein said armature is balanced statically and dynamically along its axis of rotation by said cross flexures.

28. The scanning system of claim 25 wherein said armature comprises elongated structure extending continuously between said pairs of flexures.

29. A scanning system comprising a flexure-mounted armature driven by a galvanometer to rotate about an axis, wherein said armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature, said armature being elongated, and said flexures comprising spaced apart pairs of crossed flexures, each said flexure being radially rigid, said flexures of each pair passing through and crossing said axis of rotation.

30. The scanning system of claim 29 wherein said armature is balanced statically and dynamically along its axis of rotation by said cross flexures.

31. The scanning system of claim 29 wherein said armature comprises elongated structure extending continuously between said pairs of flexures.

32. A scanning system comprising an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to rotate about an axis, wherein said armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature, said armature being elongated, and said flexures comprising spaced apart pairs of crossed flexures, each said flexure being radially rigid, said flexures of each pair passing through a cavity within said armature and crossing said axis of rotation, said armature comprising elongated structure extending continuously between said pairs of flexures, and said armature being balanced statically and dynamically along its axis of rotation by said cross flexures.

33. The scanning system of claim 24, 29 or 32 wherein the rotor of said galvanometer is polarized into two semi-cylindrical poles on opposite sides of said axis, and said galvanometer includes coils disposed on opposite sides of the magnet, separated by a plane of symmetry that is in essential alignment with the poles of the magnet at the center of its range of rotation, whereby when a current flows through the coils the magnetic field produced applies a torque to the magnet to move it a controlled distance.

34. The scanning system of claim 24, 29 or 32 wherein a sensor rotor is secured to the end of said armature opposite from said galvanometer, to determine the angular position of the armature for comparison to the command input to the system.

35. The scanning system of claim 34 wherein an optical element on said armature comprises part of an optical system of a scanning microscope.

36. The scanning system of claim 34 wherein said 5 sensor rotor is used to control said galvanometer in accordance with the command input to the system.

37. The microscope system of claim 21 further comprising an optical scanning element disposed on a flexure-mounted armature and driven by a galvanometer to 10 rotate about an axis, wherein said armature is mounted on cross-flexures in a manner to provide high angular compliance and radial rigidity and said galvanometer is of the moving magnet type having a permanent magnet rotor secured in driving relationship to said armature.

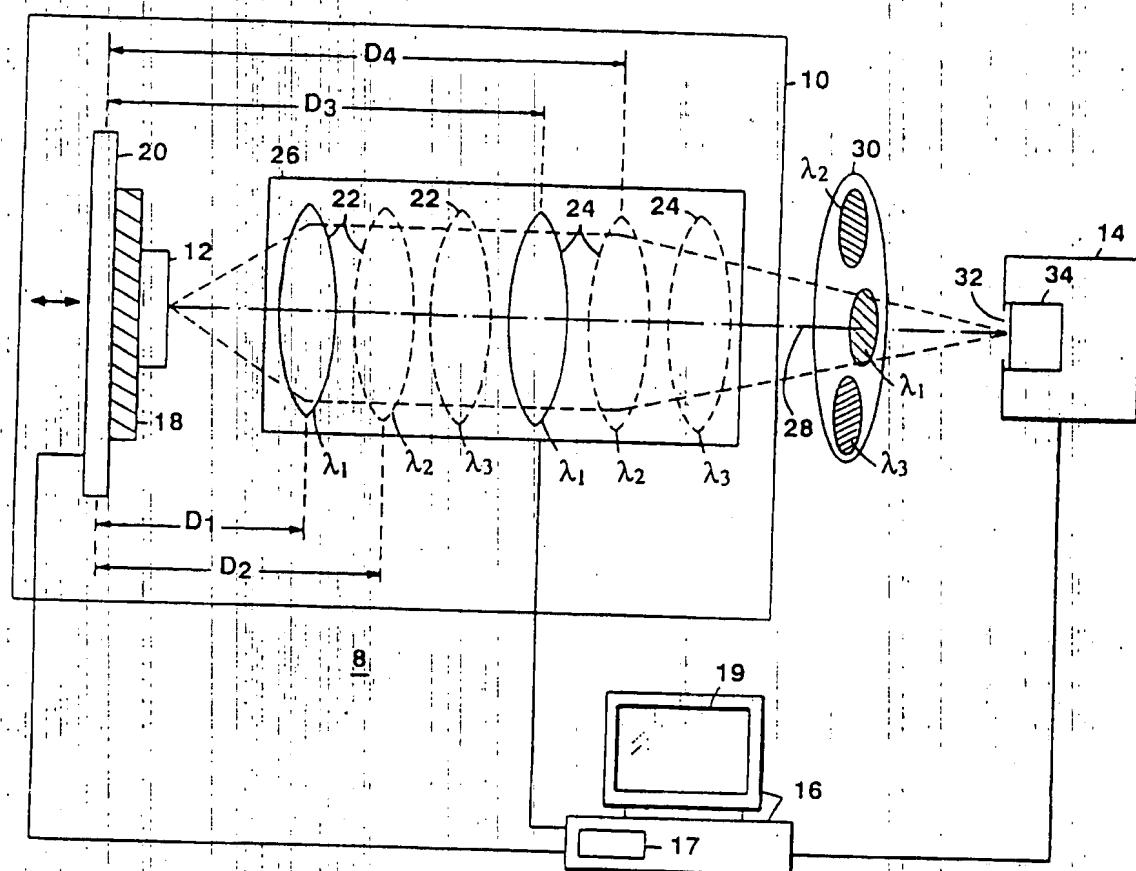


FIG. 1

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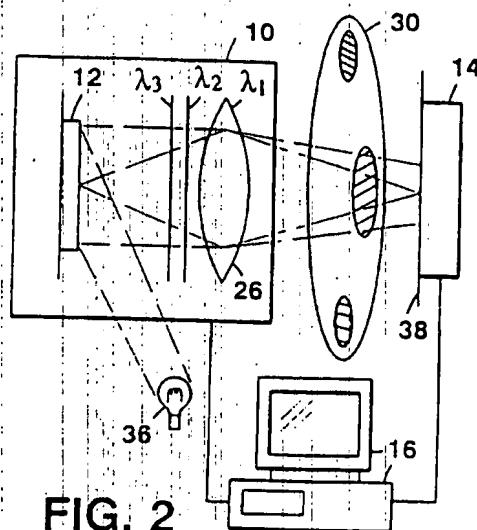


FIG. 2

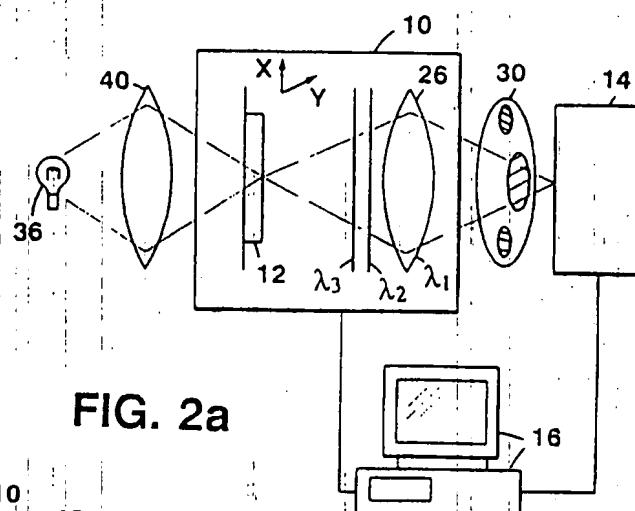


FIG. 2a

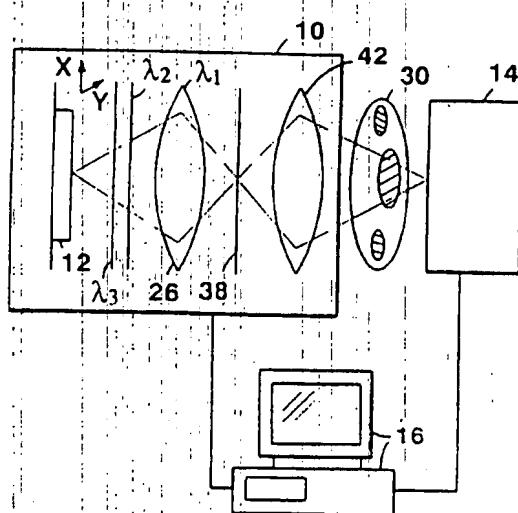


FIG. 2b

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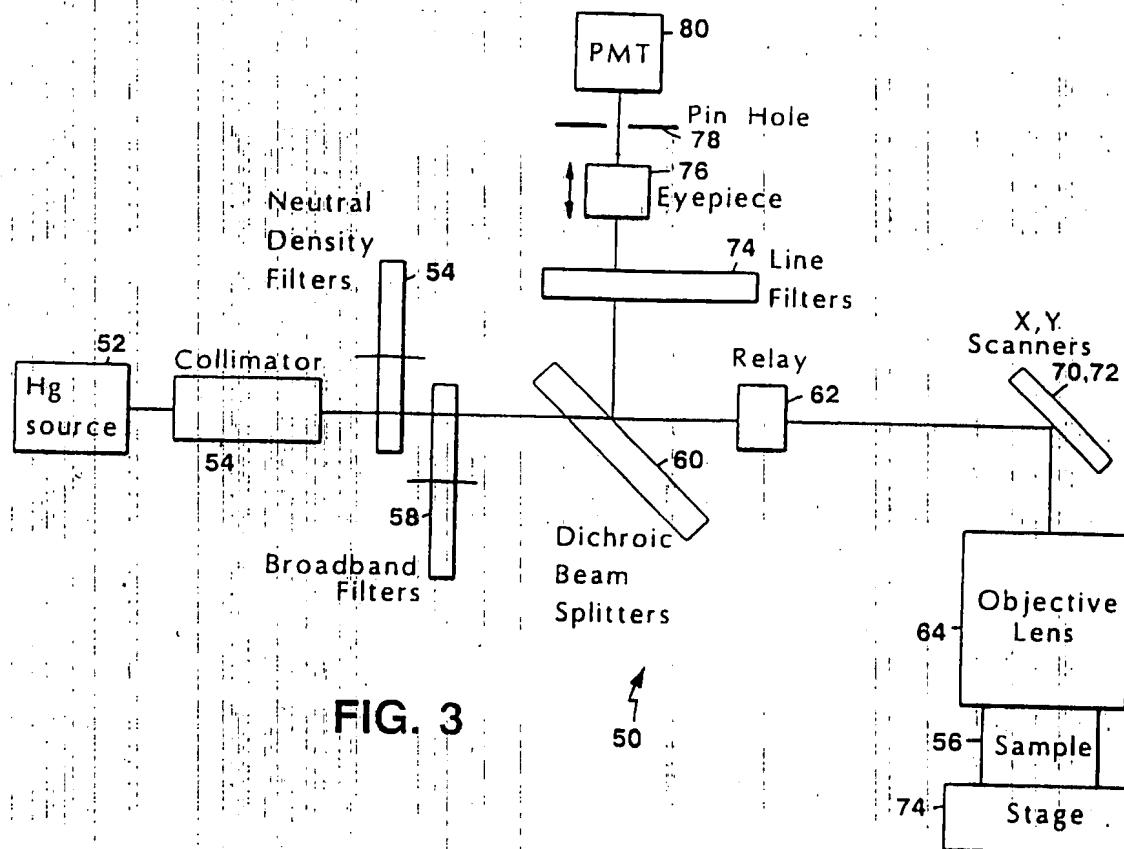


FIG. 3

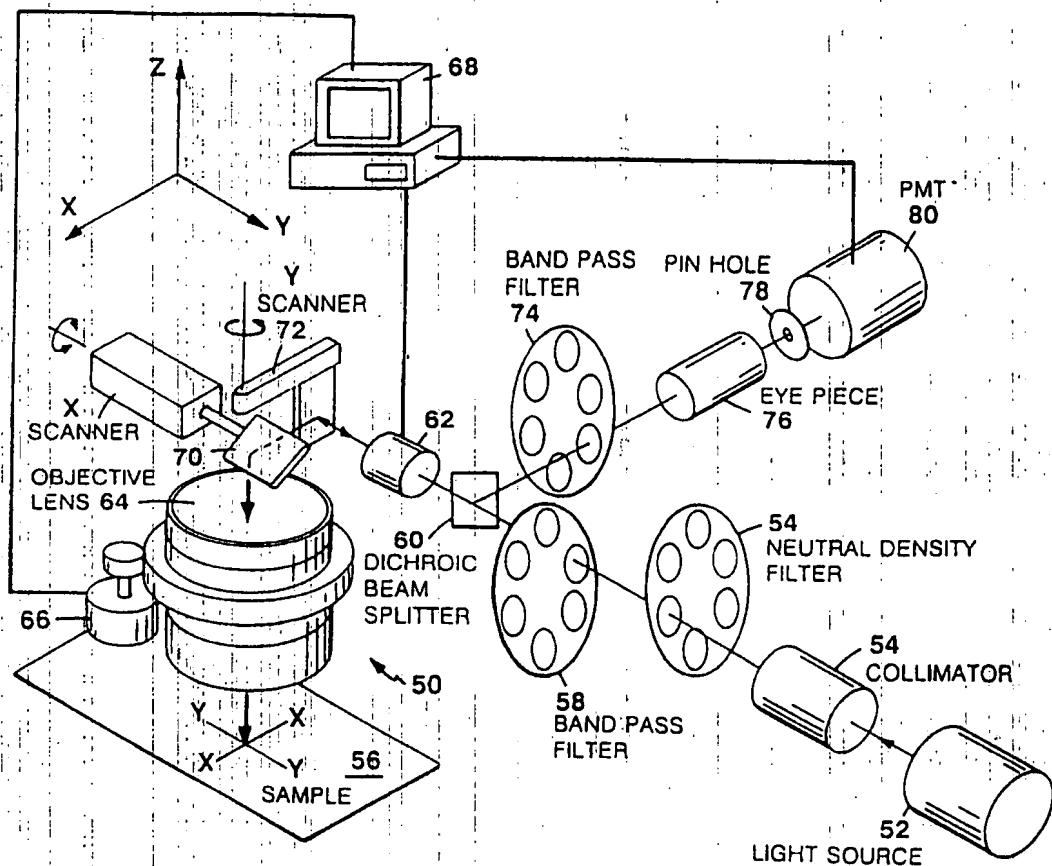
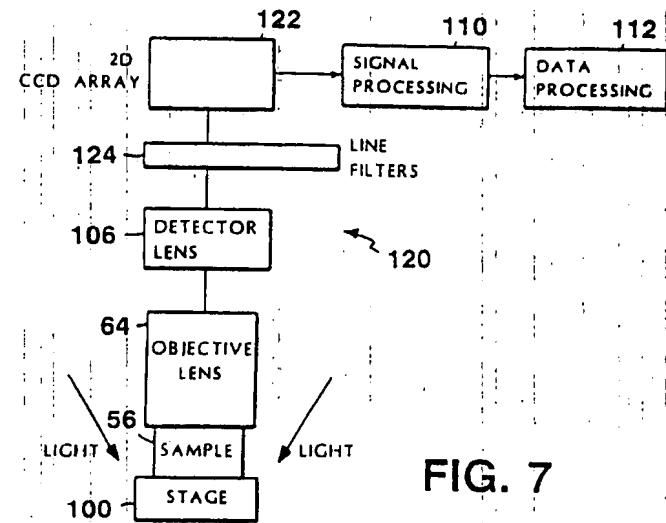
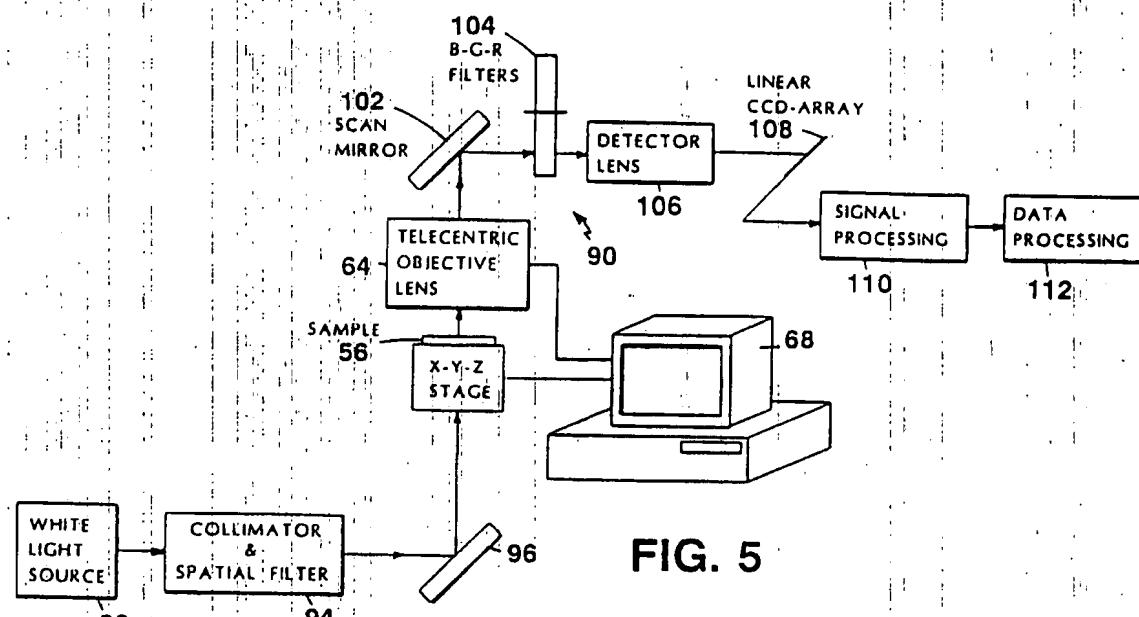


FIG. 4

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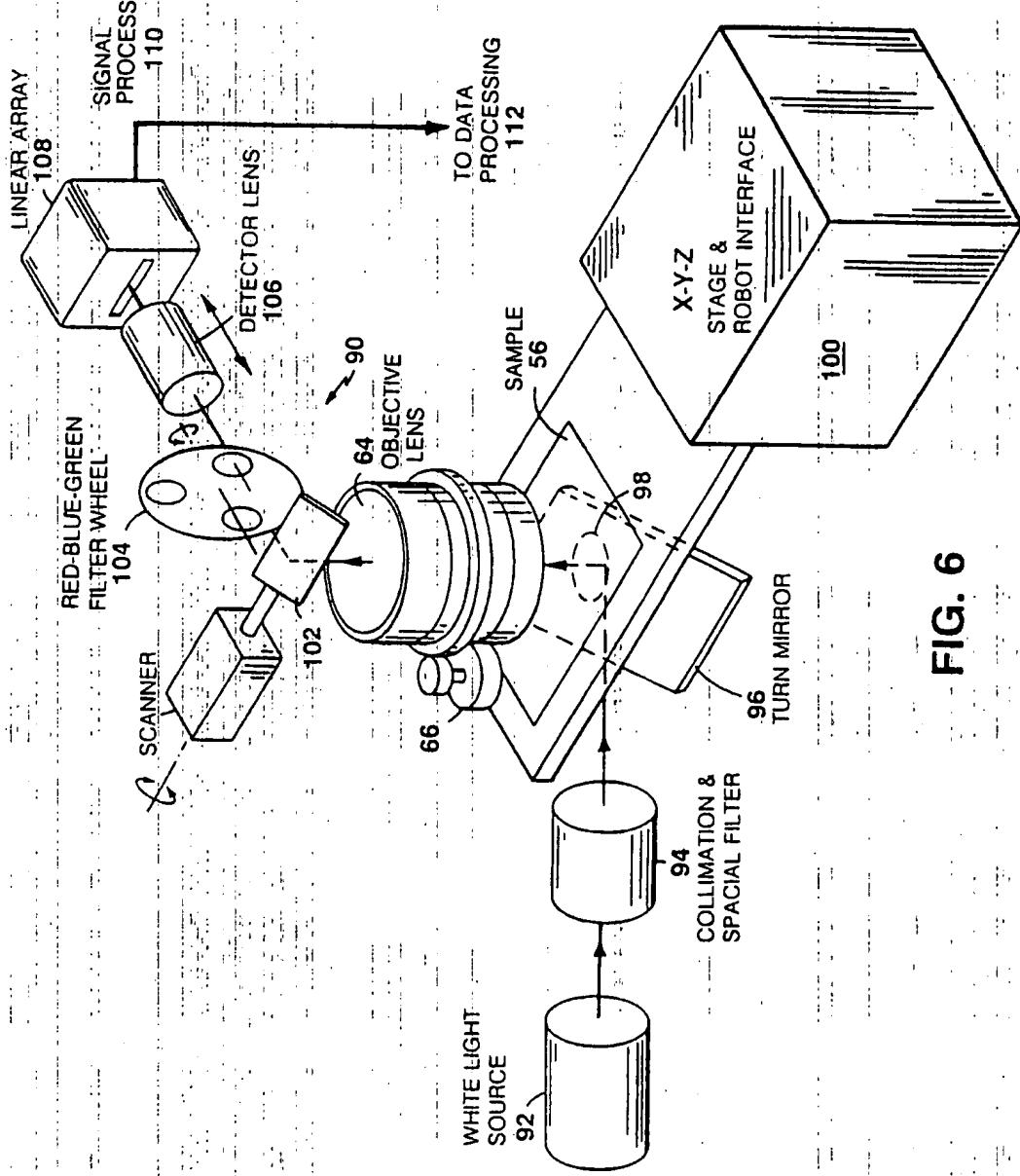


FIG. 6

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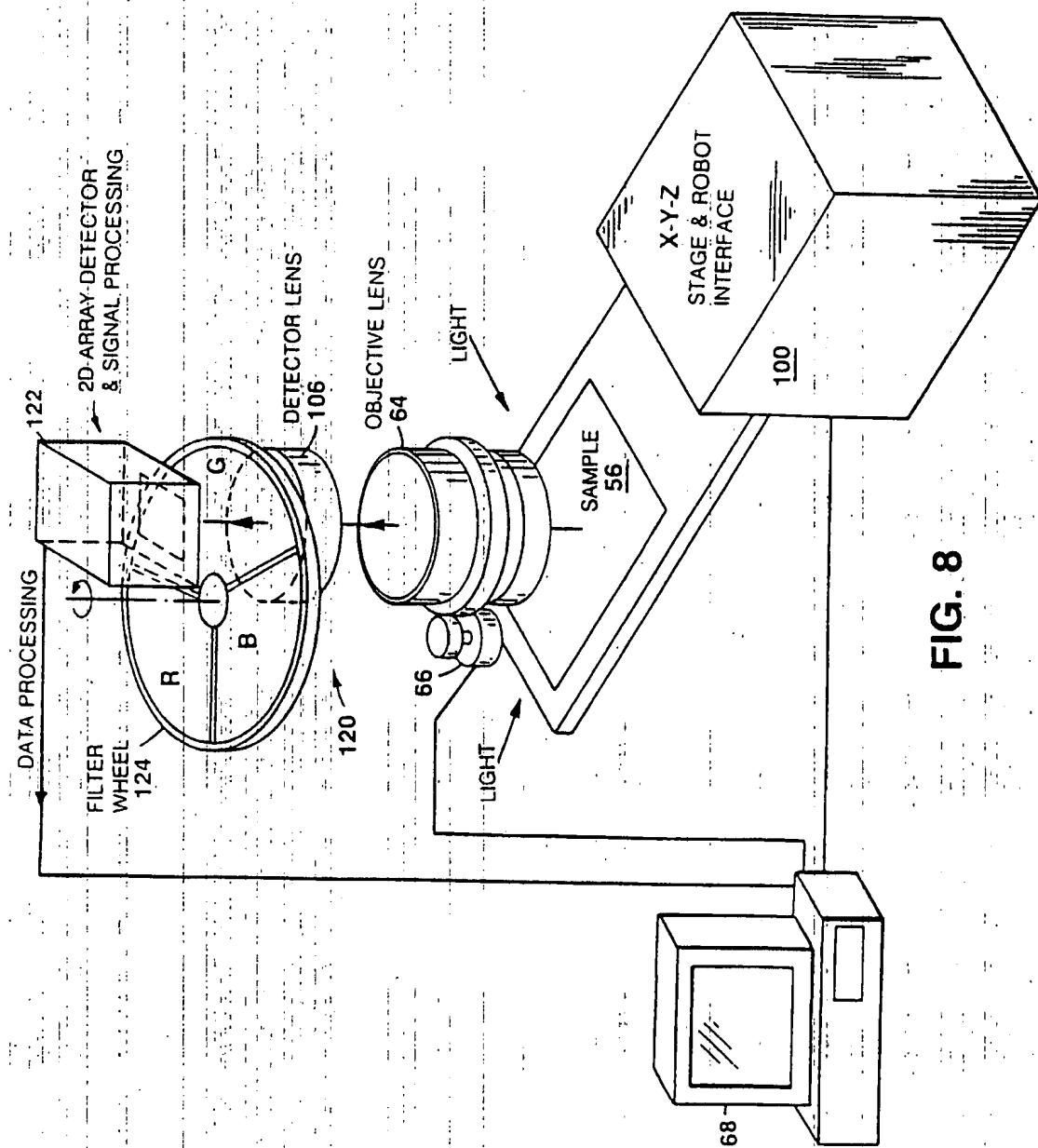


FIG. 8

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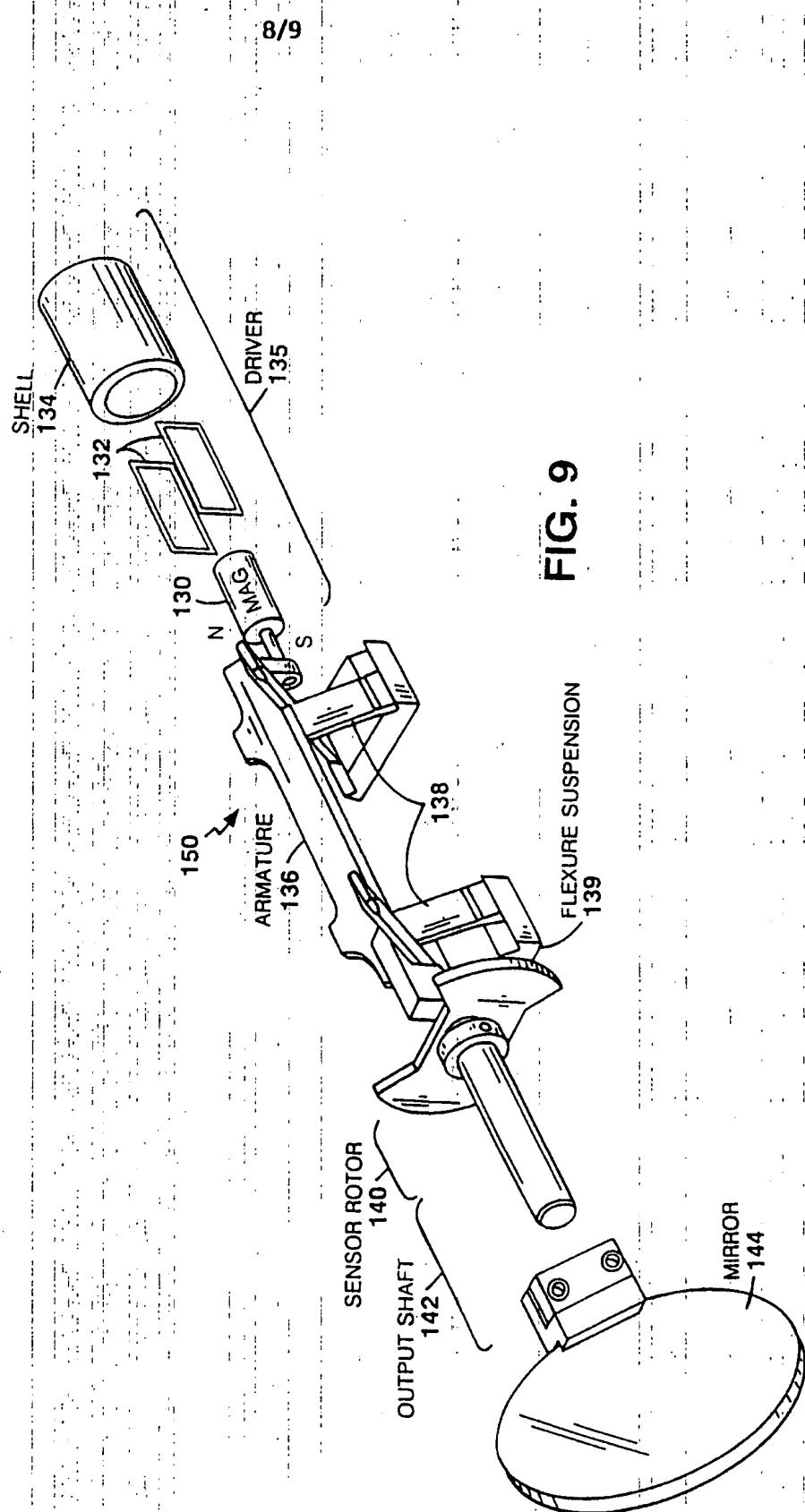


FIG. 9

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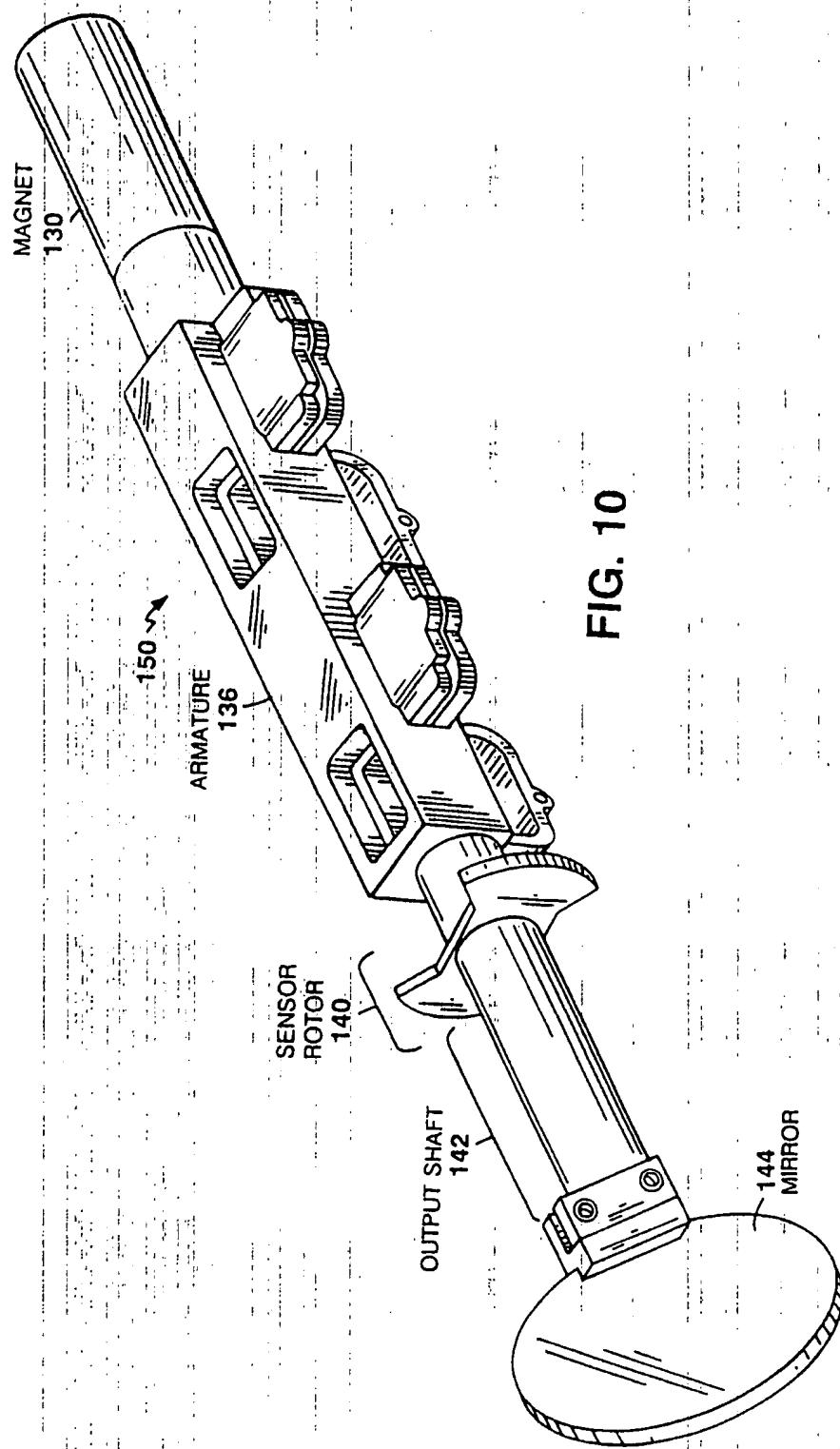


FIG. 10

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/07754

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6): G02B 26/08, 26/02, 21/00, 21/06, 21/36, 5/02.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 359/198-199, 213-214, 223-224, 363, 368-373, 379-386, 227, 236, 888-892.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,225,923 (MONTAGU) 06 JULY 1993. SEE COLUMNS 1-2 AND 4-7, AND FIGS. 1, 3, AND 5-6.	1-28.
Y	US, A, 5,340,981 (DE FORNEL ET AL) 23 AUGUST 1994. SEE COLUMNS 5-6 AND FIG. 1.	1-21.
Y	US, A, 5,532,874 (STEIN) 02 JULY 1996. SEE COLUMNS 2-3 AND FIG. 3.	1-28.
Y	US, A, 5,097,356 (PAULSER) 17 MARCH 1992. SEE COLUMNS 2-3 AND FIGS. 1 AND 3-4.	22-37.
Y	US, A, 5,247,384 (INOUE ET AL) 21 SEPTEMBER 1993. SEE COLUMNS 7-9 AND FIG. 1.	22-37.

 Further documents are listed in the continuation of Box C. See patent family annex.

Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier document published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search

20 AUGUST 1996

Date of mailing of the international search report

13 SEP 1996

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Form PCT/ISA/210 (second sheet)(July 1992)\*

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US96/07754

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	APPLIED OPTICS, VOLUME 12, NO. 10, ISSUED 01 OCTOBER 1973, J.S. COURTNEY-PRATT ET AL, "MICROSCOPE WITH ENHANCED DEPTH OF FIELD AND 3-D CAPABILITY", PAGES 2509-2519, ESPECIALLY PAGES 2509-2511 AND 2513-2514.	1-21.
A	US, A, 4,720,804 (MOORE) 19 JANUARY 1988. SEE THE WHOLE DOCUMENTATION.	1-21.
A	US, A, 4,758,727 (TOMEI ET AL) 19 JULY 1988. SEE THE WHOLE DOCUMENTATION.	1-21.
Y	JP, A, 61-281211 (TAKEUCHI ET AL) 11 DECEMBER 1986. SEE THE ENGLISH ABSTRACT AND FIG. 1.	12, AND 14-15.

**Best Available Copy**

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US96/07754

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/07754

A. CLASSIFICATION OF SUBJECT MATTER:  
US CL :

359/198-199, 213-214, 223-224, 363, 368-373, 379-386, 227, 236, 888-892.

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

APS, SCANNING(4A)MICROSCOP?, SELECT?(5A)FILTER? ARRAY(3W)(SENSOR? OR DETECTOR?), COMPUTER, (OBJECTIVE(2W)LENS)(5A)ADJUST? MONOCHROMATIC? AND ACHROMATIC?, (WAVELENGTHS OR MULTIPLE(3W)WAVELENGTH?), ARMATURE AND (FLEXURE OR FLEXIBLE); COMPUTER?(3A)(SELECT?(4A)WAVELENGTH?).

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-20, drawn to a scanning microscope having an optical system, a detector, a computer, a set of selectable insertion filters, a set of selectable insertion lenses, and a scanning mirror, classified in class 359, subclass 368+.

Group II, claims 21-23, (25-28)/22, (25-28)/23, and 37, drawn to a scanning microscope having an optical system, a detector, a computer, a set of selectable insertion filters, X and Y scanning mirrors, an optical scanning element, a specific flexure-mounted armature for supporting the optical scanning element, and a driving mechanism having a specific galvanometer for driving the armature, classified in class 359, subclass 368+.

Group III, claims 24, (25-28)/24, and 29-36, drawn to a scanning system having a specific flexure-mounted armature, and a driving mechanism having a specific galvanometer for driving the armature, classified in class 359, subclass 196+.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

First, Inventions I and (II,III) are related as combination and subcombinations. Inventions in this relationship are distinct if it can be shown that (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability and (2) that the subcombination has utility by itself or in other combination. In the instant case, the combination of Group I, claims 1-20, does not require the particulars relating to the structure of the flexure-mounted armature and the driving mechanism having a specific galvanometer as claimed in the subcombinations II and III. Further, the combination as claimed in Group I are evidence claims which indicate that the subcombination of Group II does not rely upon the specific details of the subcombination of Group III for its patentability. The subcombination of Group III has sufficient utility for operating on a scanner system or a bar code scanner. The device as claimed in Group III does not need to be used in a scanning microscope.

Second, the field of search for the above-mentioned groups are not coextensive. Group I would require a search in class 359, subclasses 368-390, and class 351 for the features relating to the filters and lenses which are selectable insertion into the optical path. Group III would require a search in class 359, subclasses 196-200 and 223-226. This group would also require a search in classes 310 and 318 for the feature relating to the structure of the galvanometer and electromagnetic driving system. Group II would require a combination of the searches in all above-mentioned classes.